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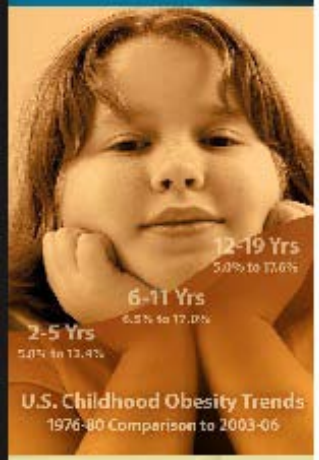

NTP Workshop: Role of Environmental Chemicals in the Development of Diabetes and Obesity

Breakout Group on

Arsenic

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Crabtree Marriott Hotel
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DEPARTMENT OF HEALTH & HUMAN SERVICES • USA

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*Not able to attend workshop due to weather-related travel delays

Does the current data from human studies of exposures to arsenic provides sufficient, limited, insufficient or non-existent evidence, or evidence to reject an association with diabetes or obesity?

- High exposure (>150 ppb): limited to sufficient evidence
- Low exposure (<150 ppb): insufficient evidence
  - Recent studies with better measures of outcome and exposure suggest association

Questions for human studies - As exposure

- Which measures of As exposure have been used in human studies of diabetes?
- For which exposure measures is the literature most informative?
- Which exposure measures are most valuable for future studies?

Human studies - As exposure

- As concentration in drinking water
  - Important for regulation
  - Sufficient to measure total As (TAs)
  - Individual measurements more informative than ecological
  - Exposures are stable for some study populations
  - Estimates of cumulative exposure using historical concentrations and durations valuable when exposure has changed over time
  - Recent studies generally have better exposure data
  - This approach will limit the range of research questions (e.g., As metabolism)

Human studies - As exposure

- Urinary biomarkers
  - Helpful to validate drinking water data
  - Integrate exposure from all sources
  - Exclusion of “fish arsenic” a major concern
  - Speciation essential: at minimum, TAs, MMA, DMA, iAs^{III}, iAs^{V}
    - Arsenic metabolites
    - Arsenobetaine
  - Growing interest and improving ability to measure methylated trivalent species, esp. DMA^{III}
    - Need for method optimization and validation studies
  - If possible, conduct field analysis of metabolites (technically challenging)

Human studies - As exposure

- Other biomarkers
  - Blood: emerging alternative to urine, but more variable
  - Nails: worthy of consideration. Non-invasive, reflect long-term exposure.
  - Target tissue (e.g., urothelial cells)
  - Other emerging biomarkers (buccal, saliva)
- Other arsenicals
  - Thioarsenicals
    - Difficult to measure- Need dual detection for sulfur and arsenic species; ppb limit of detection
  - Roxarsone
    - May be significant exposure from diet
    - Little data on content in edible chicken parts

Questions for human studies - Diabetes markers

- Which indicators of diabetes status have been used in human studies of arsenic-exposed populations?
- For which disease indicators is the literature most informative?
- Which disease indicators are most valuable for future studies?

Human studies - Diabetes markers

- Mortality relatively uninformative
- Use accepted definitions and diagnostic tools
  - History, medication
  - OGTT, HbA1c, FPG
- HbA1c and FPG becoming gold standard in field studies
  - HbA1c may require local validation for setting/country
  - Animal studies with As suggest FPG less sensitive than OGTT
- Glucosuria not recommended
- Insulin useful to examine mechanistic hypotheses
- Existing cross-sectional studies are informative, but prospective studies with incident cases desirable in future studies

What are the key sources of potential bias in studies on As and diabetes?

- Exposure measurement error
  - Fish As (increases observed As concentration)
  - Behavior change
  - Analytical concerns with urinary markers
  - Temporality in cross-sectional studies
  - Collective error expected to attenuate association
- Disease misclassification
  - Under ascertainment of diabetes in mortality data

What are the key sources of potential bias in studies on As and diabetes?

- Population selection
  - High participation and low mobility in Taiwan & Bangladesh->good internal validity
  - Differential loss of exposed cases unlikely as source of bias
  - Unknown to what extent findings from populations with high historical exposure are generalizable to current populations with lower exposures

What are the key sources of potential bias in studies on As and diabetes?

- Confounding
  - Limited evidence obesity is associated with As exposure: consider as potential modifier rather than confounder?
  - Consider co-exposure to other metals, diet, kidney function
  - Thoughtful assessment of confounding more valuable than routine control for a “laundry list” of risk factors

Animal studies

- How useful are the existing animal studies in clarifying/reducing uncertainties in the human studies?
  - Existing studies highly diverse (with respect to animal models, arsenicals and doses tested, time and routes of the exposure to As), variable in quality & relevance
  - Most not designed to examine the diabetogenic effects of chronic As exposure
  - Literature as a whole judged inconclusive, but recent studies designed to focus on diabetes better in design and quality and appear consistent with those human studies that link As exposure to diabetes

Animal studies

- Suggestive findings
  - Glucose intolerance with little effect on fasting blood glucose and insulin
  - Inhibition of adipogenesis – separating obesity from the diabetogenic effects of As
  - Low HOMA-IR (measure of insulin resistance) and low fasting plasma insulin may indicate an impairment of beta cell function

What is the strength of the mechanistic data, including the *in vitro* studies and do they support biological plausibility?

- Most not designed to study the diabetogenic effects of As; in general 3 types:
  - Using high As concentrations to examine stress response in various cell types – activation of Akt survival pathway → activation of insulin independent glucose uptake/metabolism (inconsistent with diabetes)
  - Lower As concentrations → inhibition of insulin signaling and insulin-dependent glucose uptake by adipocytes or myotubes (consistent with diabetes)
  - Using insulinoma cell lines or isolated pancreatic islets – inhibition of insulin expression and/or secretion by μM As due to oxidative damage and/or apoptosis (consistent with diabetes)

What is the best strategy to account for arsenic of seafood origin?

- Exclusion of fish eaters is effective
- Fish arsenic is a source of measurement error: statistical adjustment for fish consumption may not eliminate bias
- Cost effective strategies for analyses/markers of seafood
  As are needed

Should urine samples correct for creatinine?

- Variation in urine dilution should be considered and accounted for when indicated
- Diabetes may affect creatinine production
- Statistical adjustment preferable to standardization
- Ideally present raw and adjusted values

Does recommendation differ for Western cultures versus malnourished populations?

- No, but variations in average water consumption and urine dilution are acknowledged.

What is the potential impact of BMI in evaluating associations between arsenic and diabetes (in different populations)

- The role of BMI/obesity in the relationship of As and diabetes is of interest
- Currently little evidence that As is obesogenic
- Future studies should examine associations of As-BMI, As-diabetes in non-obese populations, and interaction of As and obesity

Suggestions for future research - Human studies

- Prospective studies including and not limited to connection with existing cohorts or follow-up of cross-sectional populations, especially lower exposure ranges
- Investigate early-life exposures
- Investigate exposure to other exposures including metals co-occurring with As
- Diet and physical activity
- Genetic susceptibility related to both As and diabetes
- Epigenetics
- Investigate potential increased risk for Type I diabetes

Suggestions for future research - Animal and *in vitro*

- Assess low-dose effects *in vitro*
- More work in epigenetic including an emphasis on developmental effects
- Identify animal models appropriate for As induced-diabetes
- Need to consider internal dose
- Look at other mechanisms of glucose homeostasis in other tissues (*in vitro*)